EXTENDED OBSERVATIONS FROM THE TODAY STUDY

Effects of Metabolic Factors, Race-Ethnicity, and Sex on the Development of Nephropathy in Adolescents and Young Adults With Type 2 Diabetes: Results From the TODAY Study

*TODAY Study Group**

Diabetes Care 2022;45:1056–1064 | https://doi.org/10.2337/dc21-1085

OBJECTIVE

To describe the longitudinal effects of sex, race-ethnicity, and metabolic factors on the risk of developing diabetic kidney disease (DKD) in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) cohort.

RESEARCH DESIGN AND METHODS

Urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) by serum creatinine and cystatin C were assessed annually for up to 15 years after study entry. Markers of DKD included micro- and macroalbuminuria (UACR ≥30 mg/g and ≥300 mg/g, respectively), hyperfiltration (eGFR ≥135 mL/min/1.73 m^2), and rapid eGFR annual decline (>3 mL/min/1.73 m^2 and/or ≥3.3%). The relationships between risk factors and DKD were evaluated longitudinally using time-to-event models.

RESULTS

Data were available on 677 participants, average age at baseline 14 years, with a mean ± SD follow-up of 10.2 ± 4.5 years. Each 1% increment in HbA_{1c} conferred higher risk of microalbuminuria (hazard ratio 1.24 [95% CI 1.18, 1.30]), macroalbuminuria (1.22, [1.11, 1.34]), hyperfiltration (1.11, [1.05, 1.17]), and rapid eGFR decline (1.12, [1.04, 1.20]). No sex or race-ethnicity differences were observed for the 14-year cumulative incidence of elevated albuminuria. Higher systolic blood pressure and baseline serum uric acid, and lower indices of β-cell function (C-peptide index and oral disposition index [oDI]), increased the risk of microalbuminuria, while higher triglycerides increased risk of micro- and macroalbuminuria. Lower oDI levels, female sex, and Hispanic ethnicity were associated with higher risk of hyperfiltration.

CONCLUSIONS

Elevated HbA_{1c} was a shared risk factor among all phenotypes of DKD in this longitudinal cohort of adolescents and young adults with youth-onset type 2 diabetes. Other risk factors included elevated blood pressure, triglycerides, serum uric acid, and β-cell dysfunction.

Corresponding author: Laure El ghormli, today@bsc.gwu.edu

Received 19 May 2021 and accepted 5 August 2021

Clinical trial reg. nos. NCT00081328, NCT01364350, NCT02310724, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.15144999.

**Members of the TODAY Study Group Writing Committee are listed in the APPENDIX. A complete list of the TODAY Study Group members can be found in the supplementary material online.*

This article is part of a special article collection available at diabetesjournals.org/journals/collection/268/Serious-Later-Risks-Associated.

See accompanying articles, p. 1038, 1046, 1049, 1065, and 1073.

In the U.S., almost half of patients with end-stage kidney disease (ESKD) have diabetic kidney disease (DKD) (1). Kidney dysfunction is frequently present at diagnosis of type 2 diabetes in youth or shortly thereafter (2). Because development of DKD relates to duration of diabetes and HbA_{1c}, the increasing number of young people diagnosed with type 2 diabetes, if not effectively treated, could dramatically add to the economic burden of this disease over the ensuing decades. Up to 45% of adolescents with type 2 diabetes are reported to progress to having ESKD as adults, with significantly greater DKD risk in adulthood when compared with youth with type 1 diabetes or with adults with type 2 diabetes (3,4).

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated that the elevated burden of DKD in youth-onset type 2 diabetes accelerated further as patients matured into young adulthood, but the determinants are not well characterized (5). We recently reported a 15-year cumulative incidence of elevated urine albumin-to-creatinine ratio (UACR) of 54.8% (5). In preliminary outcomes from the initial 5 years of the TODAY study, loss of glycemic control and hypertension conferred risk of elevated UACR, whereas insulin resistance was more predictive of hyperfiltration than conventional risk factors (2,6). Females with type 2 diabetes were found to have a threefold greater risk of developing hyperfiltration over 5 years compared with males (6). Other risk factors including BMI and elevated serum uric acid were shown to predict early findings of DKD over an average follow-up of 5.7 years (7). In this report, we provide longitudinal in-depth analyses of risk factors for DKD in the TODAY study participants followed for a mean ± SD of 10.2 ± 4.5 years.

The primary aims of this report are to examine *1*) the effects of sex and race-ethnicity and *2*) the impact of glycemic control (HbA_{1c}) and other metabolic risk factors (including BMI, blood pressure, lipids, insulin sensitivity and secretion, and serum uric acid) on the risk of DKD.

RESEARCH DESIGN AND METHODS

Study Design

A detailed description of the TODAY protocol (clinical trial reg. no. NCT00081328, ClinicalTrials.gov) and the primary outcome results have previously been published (8,9). Briefly, eligible participants (n = 699) for enrollment in the TODAY study were 10 to <18 years old with type 2 diabetes (American Diabetes Association 2002 criteria) of <2 years' duration, BMI ≥85th percentile, negative islet cell antibodies, and the presence of C-peptide (>0.6 ng/mL). Participants from 15 clinical centers were enrolled and randomly assigned to receive metformin monotherapy, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention. The primary objective of the TODAY study (2004–2011) was to evaluate the effects of the three treatment arms on time to treatment failure, defined as loss of glycemic control (HbA_{1c} ≥8% for 6 months or inability to wean from temporary insulin after acute metabolic decompensation). After an average of 3.9 years of follow-up, one-half of the cohort reached this primary end point, although the metformin plus rosiglitazone treatment arm was significantly associated with more durable glycemic control (9). As placement in the initial treatment arm had no impact on the outcomes reported in this manuscript, treatment groups were pooled for analyses.

In 2011, 572 (82%) TODAY participants enrolled in the TODAY2 postintervention follow-up study. Between 2011 and 2014, participants no longer received randomized treatment but continued to receive diabetes-related care every 3 months from the TODAY study team and were treated with metformin and/or insulin as needed to maintain glycemic control. From 2014–2020, 518 (74% of original cohort) TODAY participants transitioned to community care and continued to be followed by the TODAY study team for annual observational visits. Characteristics of the cohort were nearly identical across all study phases. TODAY and TODAY2 were approved by institutional review boards at all 15 centers, and all participants and guardians provided written informed assent and/or consent as appropriate for age and local guidelines.

Risk Factors

During the randomized trial phase of the TODAY study, participants were seen every 2 months for the first year after randomization and quarterly thereafter. During TODAY2 (2011–2020), participants were seen every 3 months for 3 years and annually for 6 years thereafter until the end of the study. Information on demographics, detailed medical history, self-reported medication usage, physical examination, and fasting laboratory studies was collected as previously described (2,8). Blood and spot urine samples were obtained after a 10- to 14-h overnight fast and processed and analyzed immediately as previously described (2). Concentrations of serum cystatin C and creatinine and urine creatinine were determined annually, using the Cystatin immunochemistry assay (Siemens Healthcare Diagnostics, Newark, DE) on a Siemens nephelometer autoanalyzer (BN II) and Creatinine Plus enzymatic Roche reagent on a Modular P analyzer (Roche Diagnostics, Indianapolis, IN) (2). Oral glucose tolerance tests were obtained after a 10- to 14-h overnight fast at baseline, months 6 and 24, annually thereafter during TODAY through 2014, and at 6 and 9 years post–randomization in TODAY2. Surrogate markers of insulin sensitivity (1/fasting insulin) and β-cell function (C-peptide index and C-peptide oral disposition index [oDI], a measure of β-cell function relative to insulin sensitivity) were calculated (10). Hypertension and dyslipidemia, all assessed longitudinally, were evaluated as previously described (5).

Kidney Outcomes

Microalbuminuria was defined as UACR ≥30 mg/g on two of three urine samples within a 6-month period through 2014 (5). In 2014–2020, microalbuminuria was defined as elevated UACR at two consecutive annual visits or as elevated UACR on reported therapy. Macroalbuminuria was defined as UACR ≥300 mg/g. Monitoring and treatment of confirmed elevated UACR were conducted as previously described (5) through 2014 with a safety oversight process with use of central data to monitor and enhance study site compliance and consistency with treatment protocols.

The full age spectrum (FAS) combined serum creatinine and cystatin C equation (FAS_{combi}), which has been validated in children and adults (11,12), was used to calculate estimated glomerular filtration rate (eGFR):

$$FAS_{combi} = \frac{107.3}{\alpha \times \frac{SCr}{Q_{crea}} + (1-\alpha) \times \frac{S_{cysC}}{Q_{cysC}}}$$

where SCr is serum creatinine, and S_{cysC} is serum cystatin C. The FAS equation is based on normalized SCr (SCr/Q) and ScysC (S_{cysC}/Q_{cysC}), where Q_{crea} is the median SCr from healthy populations, to account for age and sex, and Q_{cysC} (the median $S_{cys}C$ from healthy populations) is defined as 0.82 mg/L for ages <70 years. The coefficient α in the denominator is a weighting factor for the normalized kidney biomarkers. We used α = 0.5, which means the denominator is equal to the average of both normalized biomarkers (13).

Hyperfiltration was defined as eGFR (FAS combined equation) ≥135 mL/min/1.73 m^2 at two consecutive visits. Rapid eGFR decline was defined as an annual eGFR decline >3 mL/min/1.73 m^2 and/or ≥3.3% at two consecutive visits (14,15). Kidney Disease: Improving Global Outcomes (KDIGO) classifications were also examined (16).

Statistical Analysis

Baseline characteristics of the participants with microalbuminuria, hyperfiltration, both, or neither were compared using ANOVA *F* tests for quantitative variables and multinomial logistic regression for categorical variables. Variables with a skewed distribution were log transformed as appropriate prior to testing, and back-transformed geometric means with 95% CIs are presented in figures for continuous outcomes. The Kaplan-Meier method was used to estimate the cumulative incidence of the first occurrence of any sustained kidney outcome (microalbuminuria, macroalbuminuria, hyperfiltration, or rapid eGFR decline) and the log-rank test was used to compare incidence curves by sex and race-ethnicity. Multivariable linear mixed models, adjusted for sex, race-ethnicity, and age, were used to evaluate the effects of select risk factors on the mean of UACR or eGFR over repeated time points. Separate univariable and multivariable Cox proportional hazards regression models were used to estimate the effects of HbA_{1c} and other risk factors on the incident risk of kidney outcomes. Participants with the event at baseline were excluded from time-to-event analyses. Covariates were included in the Cox models as fixed and/or time varying as appropriate. For those with a missing covariate value at a visit, the prior observed value was carried forward. Each multivariable Cox model was adjusted for age, sex, race-ethnicity, systolic blood pressure (SBP), antihypertensive medication, BMI, and HbA_{1c}. Analyses were performed with SAS (version 9.4 for Windows; SAS Institute, Cary, NC) and considered exploratory, with statistical significance defined as $P < 0.05$.

RESULTS

Of the 699 TODAY participants enrolled in the cohort, 677 were included in the analysis. Participants subsequently found to have monogenic diabetes mutations (*n* = 22) were excluded. Data were censored at start of bariatric surgery (*n* = 28). Analyses included all available data collected at study visits during TODAY and TODAY2 for up to 15 years of follow-up (mean ± SD 10.2 ± 4.5 years).

Baseline Characteristics by DKD Outcomes

Baseline participant characteristics stratified by diagnosis of microalbuminuria and hyperfiltration status are shown in Table 1. Participants with hyperfiltration (*n* = 115) were more likely to be female and have high birth weights (>4,000 g) compared with those with a diagnosis of microalbuminuria (*n* = 87) and more likely to have a history of maternal diabetes compared with those with neither diagnosis (*n* = 175). Participants with both microalbuminuria and hyperfiltration (*n* = 133) were more likely to be of Hispanic ethnicity compared with those without DKD. Participants with both diagnoses also had higher baseline HbA_{1c}, UACR, and eGFR compared with those with neither diagnosis. Baseline UACR was similar among those with microalbuminuria with or without hyperfiltration (median = ∼11 mg/g). Baseline UACR was lower among those with only hyperfiltration or neither diagnosis (median ≈ 6.0 mg/g). Conversely, baseline eGFR was similar among those with both diagnoses or with only hyperfiltration (mean = ∼128 mL/min/1.73 min^2) but higher compared with those with only microalbuminuria or neither diagnosis (mean = ∼110–113 mL/min/1.73 min^2). Participants with microalbuminuria had lower baseline eGFR compared with those without DKD, and those with a diagnosis of hyperfiltration had lower BMI at baseline compared with all other groups.

DKD Outcomes Overall and by Sex and Race-Ethnicity

The baseline prevalence of micro- and macroalbuminuria was 8.0% and 1.5%, and the 14-year cumulative incidence was 47.3% and 15.5%, respectively. No sex or race-ethnicity differences were observed for mean UACR (Fig. 1*A* and *B*) or cumulative incidence of micro- and macroalbuminuria (Fig. 2*A*–*D* and Supplementary Table 1). In contrast, mean eGFR was higher in females compared with males and highest among Hispanics (Fig. 1*C* and *D*). The baseline prevalence of hyperfiltration was 12.3%, and the 14-year cumulative incidence was 49.2%. Cumulative incidence of hyperfiltration was also higher in females (52.2% vs. 42.5% in males; log-rank $P = 0.05$) and Hispanics (63.0% vs. 38.3% in non-Hispanic Blacks and 36.5% in non-Hispanic Whites; log-rank $P < 0.0001$) (Fig. 2*E* and *F* and Supplementary Table 1). The 14-year cumulative incidence for rapid eGFR decline was 22.9%, with no differences found by sex or race-ethnicity (Supplementary Fig. 1). There were no statistically significant associations in the development of any DKD outcomes in relation to treatment group in the TODAY trial (data not shown).

Risk Factors for Micro- and Macroalbuminuria

In univariable Cox proportional hazard ratio (HR) models (Supplementary Table 2), increases in BMI, HbA_{1c}, blood pressure (SBP and diastolic blood pressure [DBP]), eGFR, baseline serum uric acid, and log triglycerides and decreases in HDL, insulin sensitivity, and markers of β-cell dysfunction (C-peptide index and oDI) were associated with risk of microalbuminuria. Hypertension, hyperfiltration, triglyceride dyslipidemia, loss of glycemic control during the TODAY randomized clinical trial, and antihypertensive (primarily ACE inhibitor/angiotensin receptor blocker) and lipid-lowering medication use were also associated with risk of microalbuminuria.

In multivariable Cox proportional HR models, increases in HbA_{1c} (HR 1.24 [95% CI 1.18, 1.30], $P < 0.0001$), SBP (HR 1.16 [95% CI 1.03, 1.32], $P = 0.02$), log triglycerides (HR 1.30 [95% CI 1.11, 1.52], $P = 0.001$), and baseline serum uric acid (HR 1.21 [95% CI 1.06, 1.38], $P = 0.006$)

Table 1—Baseline demographic and metabolic characteristics of TODAY participants by diagnosis of elevated microalbuminuria (UACR ≥30 mg/g) or hyperfiltration during the study

Baseline characteristics	Both UACR ≥30 mg/g and hyperfiltration (*n* = 133 [26.1%])	UACR ≥30 mg/g only (*n* = 87 [17.1%])	Hyperfiltration only (*n* = 115 [22.5%])	Neither (*n* = 175 [34.3%])	*P*
Sex					
Female	90 (67.7)	44 (50.6)	83 (72.2)	111 (63.4)	0.01[a]
Male	43 (32.3)	43 (49.4)	32 (27.8)	64 (36.6)	
Race-ethnicity					
Non-Hispanic Black	39 (29.3)	40 (46.0)	32 (27.8)	64 (36.6)	0.002
Hispanic	72 (54.1)[a]	30 (34.5)	59 (51.3)	61 (34.9)[a]	
Non-Hispanic White	17 (12.8)	15 (17.2)	21 (18.3)	42 (24.0)	
Other	5 (3.8)	2 (2.3)	3 (2.6)	8 (4.6)	
Age (years)	13.8 ± 2.0	14.1 ± 2.2	13.6 ± 1.9	14.1 ± 1.9	0.12
Type 2 diabetes duration (months)	8.0 ± 6.3	8.5 ± 6.2	7.7 ± 5.8	7.5 ± 5.9	0.32
Maternal diabetes	58 (48.7)	37 (45.7)	59 (53.2)	54 (32.7)	0.003[b]
Birth weight					
Small (<2,500 g)	13 (14.0)	6 (9.5)	4 (5.5)	11 (8.3)	0.03[a]
Normal (2,500–4,000 g)	60 (64.5)	52 (82.5)	48 (65.7)	102 (76.7)	
Large (>4,000 g)	20 (21.5)	5 (7.9)	21 (28.8)	20 (15.0)	
BMI (kg/m^2)	35.1 ± 6.9	37.9 ± 8.8	31.8 ± 6.6	35.0 ± 7.5	<0.0001[abc]
HbA_{1c} (%)	6.1 ± 0.8	6.1 ± 0.8	5.9 ± 0.7	5.9 ± 0.6	0.009[d]
UACR (mg/g)*	11.0 [22.0]	11.5 [28.0]	6.0 [4.0]	6.0 [5.0]	<0.0001[abce]
eGFR (mL/min per 1.73 min^2)	128.3 ± 15.8	110.4 ± 12.4	128.7 ± 14.8	113.0 ± 13.0	<0.0001[bcef]

Data are *n* (%), mean ± SD, or median [interquartile range]. Approximately 25% of the 677 participants included in the study did not have serum creatinine values assessed at baseline; thus, eGFR and hyperfiltration could not be calculated (data from *n* = 510 participants included). Information on history of maternal diabetes and participant birth weight was not available for all *n* = 510 participants; all other data were complete, with overall *N* of participants for each variable shown in the column headers. *Based on log-transformed value for testing. Post hoc Bonferroni-adjusted pairwise comparisons were performed when an overall difference was found ($P < 0.05$) and indicated with different letter superscripts: [a]UACR ≥30 mg/g only vs. hyperfiltration only; [b]hyperfiltration only vs. neither; [c]both vs. hyperfiltration only; [d]both vs. neither; [e]UACR ≥30 mg/g only vs. neither; [f]both vs. UACR ≥30 mg/g only.

and decreases in insulin sensitivity (HR 0.85 [95% CI 0.74, 0.96], $P = 0.01$) and secretion (C-peptide oDI) (HR 0.80 [95% CI 0.69, 0.93], $P = 0.004$) remained associated with greater risk of microalbuminuria (Table 2).

Similar associations were observed for risk of macroalbuminuria (Supplementary Table 2), with a few notable differences: BMI, eGFR, lipid-lowering medication, and HDL did not relate to risk of macroalbuminuria in univariable models. After multivariable adjustments, increases in HbA_{1c} (HR 1.22 [95% CI 1.11, 1.34], $P < 0.0001$) and log triglycerides (HR 1.49 [95% CI 1.17, 1.88], $P = 0.001$) remained associated with risk of macroalbuminuria (Table 2), and maternal diabetes and small birth weight (<2,500 g) were independently associated with risk of macroalbuminuria (Supplementary Table 2).

Risk Factors for Hyperfiltration and Rapid eGFR Decline

In univariable Cox proportional HR models (Supplementary Table 3), maternal diabetes and large birth weight (>4,000 g) were associated with risk of hyperfiltration. In addition, higher HbA_{1c} and log triglycerides and decreases in β-cell function (C-peptide index and oDI) were associated with risk of hyperfiltration in univariable models. After multivariable adjustments, HbA_{1c} (HR 1.11 [95% CI 1.05, 1.17], $P = 0.0002$) and C-peptide oDI (HR 0.77 [95% CI 0.65, 0.90], $P = 0.001$) remained significant risk factors for hyperfiltration, along with female sex (HR 1.38 [95% CI 1.01, 1.91], $P = 0.04$) and Hispanic ethnicity (HR 1.78 [95% CI 1.19, 2.68], $P = 0.005$) (Table 3).

Increases in HbA_{1c}, blood pressure (SBP and DBP), and log UACR, as well as ACE inhibitor/angiotensin receptor blocker use, loss of glycemic control during the TODAY randomized clinical trial, hypertension, and microalbuminuria, were associated with risk of rapid eGFR decline in univariable models (Supplementary Table 3). After multivariable adjustments, HbA_{1c} (HR 1.12 [95% CI 1.04, 1.20], $P = 0.004$) remained associated with risk of rapid eGFR decline but not blood pressure or log UACR (Table 3). Hyperfiltration was not significantly associated with risk of rapid eGFR decline in a univariable Cox model (HR 1.46 [95% CI 0.96, 2.23], $P = 0.08$); however, after multivariable adjustments for age, sex, and race-ethnicity, hyperfiltration was associated with a significantly higher risk of rapid eGFR decline (HR 1.66 [95% CI 1.08, 2.55], $P = 0.02$).

Longitudinal Associations of UACR and eGFR With Clinical Risk Factors

UACR and eGFR, as continuous variables, positively correlated with increases in common clinical risk factors over time, except for BMI (Supplementary Fig. 2).

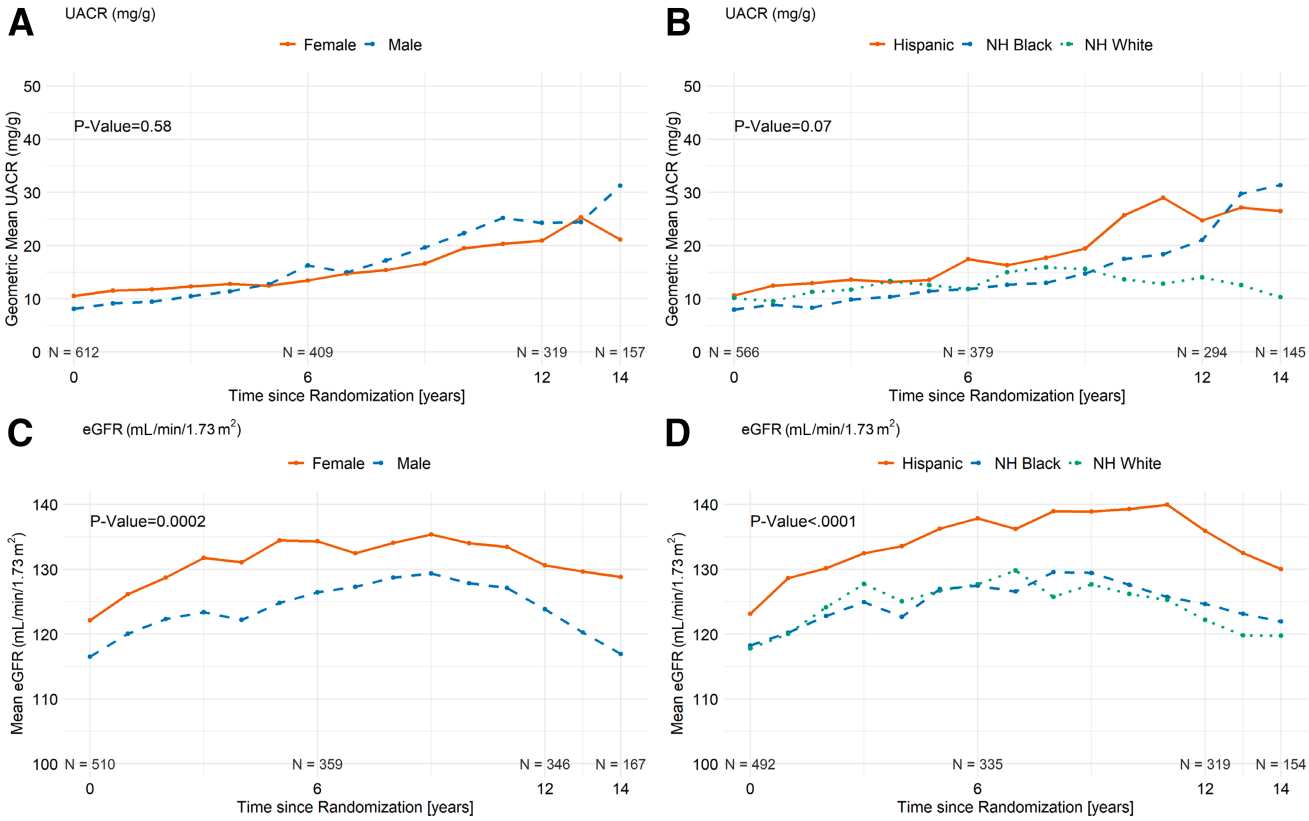

Figure 1—DKD outcomes (mean UACR and eGFR) by sex and race-ethnicity over time. Mean DKD outcomes: for up to 14 years of follow-up. Data from the "other" race-ethnicity group not included due to small numbers. NH, non-Hispanic.

Notable positive associations were observed between UACR and blood pressure (SBP and DBP) and triglycerides, while modest associations were observed between HbA_{1c} and eGFR.

Chronic Kidney Disease Risk by KDIGO Classification

For UACR, 64% of participants were in the optimal to high normal range, whereas 24% were at high risk and 12% at very high and nephrotic range (Supplementary Fig. 3). For eGFR, 95% were in the high and optimal eGFR range, 4% in mild impairment range, and $<$1% in severe impairment range.

CONCLUSIONS

Findings from the current analyses examining risk factors for DKD progression in youth-onset type 2 diabetes demonstrate that HbA_{1c}, blood pressure, triglycerides, and baseline serum uric acid relate to risk of elevated UACR, while HbA_{1c} independently conferred risk of hyperfiltration and rapid eGFR decline. Female sex and Hispanic ethnicity associated with risk of hyperfiltration, and maternal diabetes magnified risk of macroalbuminuria and hyperfiltration. β-Cell dysfunction remained a significant risk factor for microalbuminuria and hyperfiltration, even after adjustment for potential confounders such as HbA_{1c}.

Youth-onset type 2 diabetes has been associated with higher risk for DKD and ESKD than adult-onset type 2 diabetes and type 1 diabetes (3,4). In the linkage of the Australian National Death Index with the comprehensive Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), it was reported that type 2 diabetes diagnosed prior to 30 years of age was associated with a substantially higher risk for ESKD by 40 years of diabetes duration despite initially better baseline kidney function and less ESKD in the first 10–15 years of diabetes. In the SEARCH for Diabetes in Youth (SEARCH) study, investigators found a greater than twofold odds of having DKD among adolescents with type 2 diabetes compared with those with type 1 diabetes (17). The results of TODAY and TODAY2 support these data by showing a uniquely high burden of DKD, with $>$50% of participants with youth-onset type 2 diabetes developing DKD by, on average, 10 years of follow-up (5).

DKD stems from glomerular and tubular damage sustained from a combination of risk factors including hyperglycemia. Poor glycemic control provokes structural kidney injuries including glomerular and tubular basement membrane thickening, mesangial and interstitial matrix expansion, tubular atrophy, and glomerular sclerosis (18,19). Consistent with our data in TODAY and TODAY2, the Diabetes Control and Complications Trial (DCCT) and follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) studies as well as the Oxford Regional Prospective Study of young adults with type 1 diabetes have conclusively established that hyperglycemia is directly associated with DKD (2,20,21). In addition to hyperglycemia, hypertension has been shown to accentuate progression of DKD (22,23). Sexual dimorphism may also play a key role in the pathogenesis of DKD, yet the data on sex and DKD risk are inconsistent. In TODAY and TODAY2, the cumulative incidence of hyperfiltration was higher in females and Hispanics, although no differences were observed

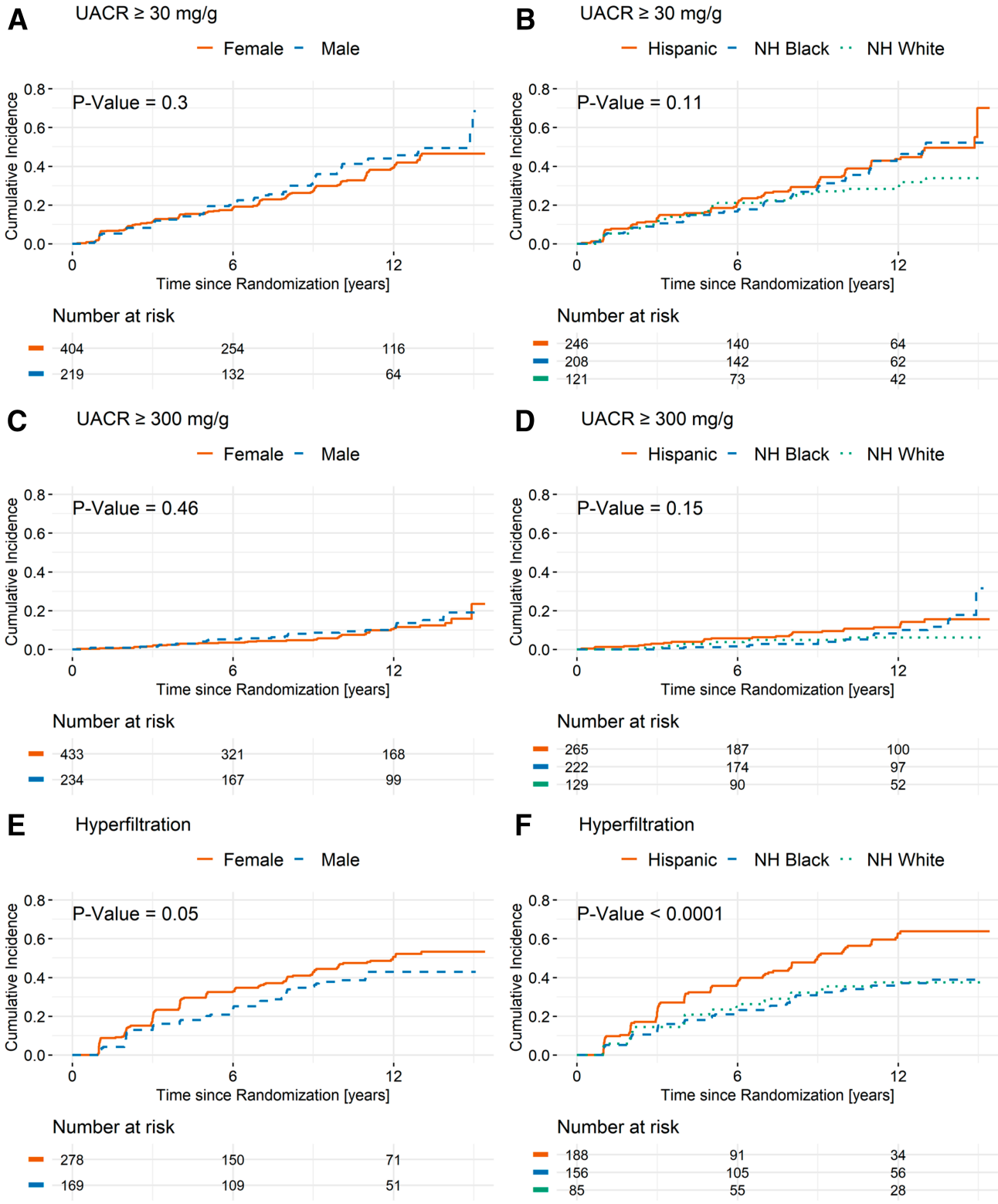

Figure 2—Cumulative incidence of DKD outcomes (microalbuminuria, UACR ≥30 mg/g; macroalbuminuria, UACR ≥300 mg/g; and hyperfiltration) by sex and race-ethnicity. Kaplan-Meier cumulative incidence curves for the DKD outcomes, with number of participants at risk at 0, 6, and 12 years. The number at risk beyond year 12 declines as a function of staggered entry into the cohort from 2004 to 2008. *P* value for difference by sex and race-ethnicity based on log-rank test. Data from the "other" race-ethnicity group are not included due to small numbers. NH, non-Hispanic.

for micro- or macroalbuminuria or rapid eGFR decline. Other DKD studies have reported a higher risk in men (24), a higher risk in women (20,25,26), or no sexual dimorphism (27). Due to the lack of measured glomerular filtration rate, we cannot rule out that the sex and race/ethnicity differences that we observed for eGFR were a function of serum

Table 2—Multivariable Cox proportional hazards models predicting microalbuminuria (UACR ≥30 mg/g) and macroalbuminuria (UACR ≥300 mg/g)

	UACR ≥30 mg/g			UACR ≥300 mg/g		
Characteristics (reference group or unit change)	HR	95% CI	*P*	HR	95% CI	*P*
Sex (female vs. male)	1.07	0.80, 1.43	0.63	1.04	0.60, 1.80	0.88
Race/ethnicity (vs. non-Hispanic White)						
Non-Hispanic Black	1.04	0.68, 1.60	0.84	1.26	0.50, 3.21	0.62
Hispanic	1.36	0.90, 2.07	0.15	2.03	0.83, 5.02	0.12
Age (per year)	0.96	0.90, 1.03	0.30	0.91	0.80, 1.03	0.14
BMI (per 5 kg/m^2)	1.06	0.98, 1.15	0.14	0.89	0.75, 1.06	0.20
HbA_{1c} (per %)	1.24	1.18, 1.30	<0.0001	1.22	1.11, 1.34	<0.0001
SBP (per 10 mmHg)	1.16	1.03, 1.32	0.02	1.16	0.93, 1.44	0.20
eGFR (per 10 mL/min/1.73 m^2)	1.01	0.94, 1.08	0.77	0.97	0.87, 1.09	0.65
Log triglycerides (per SD)	1.30	1.11, 1.52	0.001	1.49	1.17, 1.88	0.001
Log insulin sensitivity (per SD)	0.85	0.74, 0.96	0.01	0.89	0.71, 1.11	0.29
Log C-peptide oDI (per SD)	0.80	0.69, 0.93	0.004	0.80	0.62, 1.04	0.09
Baseline serum uric acid (per mg/dL)	1.21	1.06, 1.38	0.006	1.13	0.87, 1.48	0.35

HRs (with 95% CIs and *P* values) per reference group or unit change (as indicated) in separate Cox proportional hazards model predicting the risk of UACR ≥30 mg/g or UACR ≥300 mg/g during the study. Each model is minimally adjusted for age, sex, race-ethnicity, SBP, BMI, reported use of antihypertensive medication, and HbA_{1c}. Factors are entered as fixed (sex, race-ethnicity, age at baseline, baseline serum uric acid) or as time-dependent (all other factors, assessed or measured at, or at the most recent visit up to, the particular time of the event or right censoring time) covariates in the models.

creatinine and cystatin C rather than actual differences in filtration. A relationship between birth weights <2,500 g and risk for DKD by young adulthood has also been described in Pima Indians with type 2 diabetes where higher prevalence of DKD was noted in both the low and high birth weight groups (28). This relationship may relate to insulin resistance, as low birth weight has been associated with increased insulin resistance, whereas high birth weight is associated with higher risk of obesity (29). In the current study, high birth weights were more prevalent in participants who experienced hyperfiltration compared with those who did not. Other important risk factors for the development and progression of DKD in young persons with diabetes include elevated LDL cholesterol and/or triglycerides (30) and serum uric acid (7). Timely

Table 3—Multivariable Cox proportional hazards models predicting hyperfiltration and rapid eGFR decline

	Hyperfiltration			Rapid eGFR decline		
Characteristics (reference group or unit change)	HR	95% CI	*P*	HR	95% CI	*P*
Sex (female vs. male)	1.38	1.01, 1.91	0.04	1.16	0.74, 1.82	0.41
Race/ethnicity (vs. non-Hispanic White)						
Non-Hispanic Black	0.85	0.54, 1.33	0.46	0.90	0.52, 1.59	0.73
Hispanic	1.78	1.19, 2.68	0.005	0.60	0.33, 1.08	0.09
Age (per year)	0.99	0.92, 1.07	0.8	1.06	0.95, 1.18	0.31
BMI (per 5 kg/m^2)	0.96	0.87, 1.05	0.34	0.88	0.76, 1.02	0.09
HbA_{1c} (per %)	1.11	1.05, 1.17	0.0002	1.12	1.04, 1.20	0.004
SBP (per 10 mmHg)	1.02	0.89, 1.17	0.76	1.16	0.96, 1.40	0.13
Log UACR (per SD)	0.97	0.81, 1.16	0.75	1.18	0.93, 1.50	0.17
Log triglycerides (per SD)	1.16	0.98, 1.37	0.09	0.94	0.74, 1.19	0.57
Log insulin sensitivity (per SD)	1.02	0.87, 1.18	0.83	1.14	0.92, 1.40	0.23
Log C-peptide oDI (per SD)	0.77	0.65, 0.90	0.001	1.10	0.87, 1.41	0.42

HRs (95% CIs and *P* values) per reference group or unit change (as indicated) in separate Cox proportional hazards model predicting the risk of hyperfiltration and rapid eGFR decline during the study. Each model is minimally adjusted for age, sex, race-ethnicity, SBP, BMI, reported use of antihypertensive medication, and HbA_{1c}. Factors are entered as fixed (sex, race-ethnicity, age at baseline) or as time-dependent (all other factors, assessed or measured at, or at the most recent visit up to, the particular time of the event or right censoring time) covariates in the models.

identification of individuals at risk for DKD is critical to initiate kidney protective pharmacotherapies and possibly reverse the early stages of DKD.

Despite the high burden of kidney dysfunction in youth-onset type 2 diabetes, there is optimism for kidney-protective pharmacotherapies to mitigate risk for DKD. For adults with type 2 diabetes, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to attenuate albuminuria and reduce DKD progression, including delaying ESKD by >15 years or avoiding it entirely (31–33). Glucagon-like peptide 1 (GLP-1) receptor agonists have also demonstrated attenuation of albuminuria in cardiovascular outcome trials (34). Finally, the Study Of Diabetic Nephropathy With Atrasentan (SONAR) trial, a randomized controlled clinical trial to evaluate the long-term effects of the selective endothelin A receptor antagonist astrasentan, demonstrated reduction in the doubling of serum creatinine or ESKD by 35% in participants with type 2 diabetes and elevated albuminuria over follow-up of 2.1 years (35).

The approval of newer type 2 diabetes therapies that impact both weight reduction and glycemic control in youth with obesity and type 2 diabetes has the potential to improve kidney outcomes, but the cardiovascular and kidney outcome trials have been limited to adults with type 2 diabetes. It remains unclear whether or how these findings will translate to youth or young adults with type 2 diabetes. Safety and efficacy trials with SGLT2 inhibitors and GLP-1 receptor agonists are ongoing, and there are limited data published.

Although liraglutide is approved for use in youth-onset type 2 diabetes for glycemic control (36), it remains unclear whether GLP-1 receptor agonists can also mitigate progression of DKD in youth with type 2 diabetes. SGLT2 inhibitors and endothelin receptor antagonists are thought to confer greater kidney protection than GLP-1 receptor agonists but are not yet approved in youth-onset type 2 diabetes. The cumulative TODAY studies data underscore the complexity of risks factors implicated in the accelerated risk for development of early DKD in youth-onset type 2 diabetes, and combination therapies or interventions that address several risk factors are likely needed to effectively impede progression of DKD (37).

The TODAY studies have important strengths and limitations. Limitations include the use of eGFR and insulin sensitivity in lieu of direct measurements, such as repeated gold standard assessments of GFR and insulin sensitivity, although such arduous methods would pose many challenges across multiple sites in a large, long-term longitudinal study of youth. Additionally, our data were limited to random UACR collections instead of timed urine collections, and there were limited events of chronic kidney disease to allow for analyses. There are several strengths of this multicenter study, including long-term retention and follow-up of a unique cohort of participants with youth-onset type 2 diabetes who were comprehensively and regularly phenotyped and racially diverse. Prompt recruitment of youth diagnosed with type 2 diabetes within 2 years (and on average <8 months) of onset in the TODAY study is a strength. The relatively large number of participants with youth onset with available data at several times points for eGFR and UACR is unique and allowed us to delineate risk factors for discrete DKD phenotypes.

In conclusion, adolescents with type 2 diabetes exhibit a high risk for DKD over a mean ± SD follow-up of 10.2 ± 4.5 years. Elevated HbA_{1c} was a shared risk factor among microalbuminuria, macroalbuminuria, hyperfiltration, and rapid eGFR decline in youth-onset type 2 diabetes. We also identified distinct risk factors for these DKD phenotypes, arguing for targeted surveillance for young persons with type 2 diabetes who exhibit these risk factors. In utero diabetes exposure and birth weight associations underscore the need to monitor and attenuate pregnancy-related risk fac-tors to impede the development of DKD. Finally, adjunctive therapeutic strategies that can target associated risk factors hold promise to mitigate the progression of DKD in youth-onset type 2 diabetes.

APPENDIX

TODAY Study Group Writing Committee. Petter Bjornstad (University of Colorado Anschutz Medical Campus, Aurora, CO), Laure El ghormli (The Biostatistics Center, The George Washington University, Rockville, MD), Kara S. Hughan (UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA), Lori M. Laffel (Joslin Diabetes Center, Boston, MA), Kristen J. Nadeau (University of Colorado Anschutz Medical Campus, Aurora, CO), Maria Rayas (UT Health San Antonio, San Antonio, TX), Bereket Tesfaldet (The Biostatistics Center, The George Washington University, Rockville, MD), Sherida E. Tollefsen (St. Louis University Health Sciences Center, St. Louis, MO), Steven M. Willi (Children's Hospital of Philadelphia, Philadelphia, PA), and Jane Lynch (UT Health San Antonio, San Antonio, TX).

Acknowledgments. The authors gratefully acknowledge the participation and guidance of the American Indian partners associated with the clinical center located at the University of Oklahoma Health Sciences Center, including members of the Absentee Shawnee Tribe, Cherokee Nation, Chickasaw Nation, Choctaw Nation of Oklahoma, and Oklahoma City Area Indian Health Service.

The opinions expressed in this manuscript are those of the authors and do not necessarily reflect the views of the respective Tribes or the Indian Health Service.

Funding. This work was completed with funding from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institutes of Health Office of the Director through grants U01-DK61212, U01-DK61230, U01-DK61239, U01-DK61242, and U01-DK61254.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The NIDDK project office was involved in all aspects of the study, including design and conduct; collection, management, analysis, and interpretation of the data; review and approval of the manuscript; and decision to submit the manuscript for publication.

Duality of Interest. The TODAY Study Group thanks the following companies for donations of materials in support of the study's efforts: Becton, Dickinson and Company, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, LifeScan, Inc., Pfizer, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.B. and J.L. wrote the manuscript. L.E. conducted the statistical analyses and contributed to data interpretation and writing. K.S.H., L.M.L., K.J.N., M.R., B.T., S.E.T., and S.M.W. contributed to study and manuscript design, data interpretation, and manuscript edits. L.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Saran R, Li Y, Robinson B, et al.; US Renal Data System 2015 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2016;67(3 Suppl. 1):Svii, S1–305
2. TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013;36:1735–1741
3. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 2006;296:421–426
4. Morton JI, Liew D, McDonald SP, Shaw JE, Magliano DJ. The association between age of onset of type 2 diabetes and the long-term risk of end-stage kidney disease: a national registry study. Diabetes Care 2020;43:1788–1795
5. TODAY Study Group. Long-term complications in youth-onset type 2 diabetes. N Engl J Med 2021;385:416–426
6. Bjornstad P, Nehus E, El Ghormli L, et al.; TODAY Study Group. Insulin sensitivity and diabetic kidney disease in children and adolescents with type 2 diabetes: an observational analysis of data from the TODAY clinical trial. Am J Kidney Dis 2018;71:65–74
7. Bjornstad P, Laffel L, Lynch J, et al.; TODAY Study Group. Elevated serum uric acid is associated with greater risk for hypertension and diabetic kidney diseases in obese adolescents with type 2 diabetes: an observational analysis from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. Diabetes Care 2019;42:1120–1128
8. Zeitler P, Epstein L, Grey M, et al.; TODAY Study Group. Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. Pediatr Diabetes 2007;8:74–87
9. Zeitler P, Hirst K, Pyle L, et al.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247–2256
10. Bacha F, Pyle L, Nadeau K, et al.; TODAY Study Group. Determinants of glycemic control in youth with type 2 diabetes at randomization in the TODAY study. Pediatr Diabetes 2012;13:376–383
11. Bacchetta J, Cochat P, Rognant N, Ranchin B, Hadj-Aissa A, Dubourg L. Which creatinine and cystatin C equations can be reliably used in children? Clin J Am Soc Nephrol 2011;6:552–560
12. Fadrowski JJ, Neu AM, Schwartz GJ, Furth SL. Pediatric GFR estimating equations applied to adolescents in the general population. Clin J Am Soc Nephrol 2011;6:1427–1435
13. Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant 2016;31:798–806
14. Krolewski AS, Niewczas MA, Skupien J, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care 2014;37:226–234
15. Bjornstad P, Cherney DZ, Snell-Bergeon JK, et al. Rapid GFR decline is associated with renal hyperfiltration and impaired GFR in adults with type 1 diabetes. Nephrol Dial Transplant 2015;30:1706–1711
16. Stevens PE; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825–830
17. Dabelea D, Stafford JM, Mayer-Davis EJ, et al.; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017;317:825–835
18. Afkarian M. Diabetic kidney disease in children and adolescents. Pediatr Nephrol 2015;30:65–74
19. Ekinci EI, Jerums G, Skene A, et al. Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care 2013;36:3620–3626
20. DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014;2:793–800
21. Amin R, Turner C, van Aken S, et al. The relationship between microalbuminuria and glomerular filtration rate in young type 1 diabetic subjects: The Oxford Regional Prospective Study. Kidney Int 2005;68:1740–1749
22. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 1995;123:754–762
23. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412–419
24. de Hauteclocque A, Ragot S, Slaoui Y, et al.; SURDIAGENE Study group. The influence of sex on renal function decline in people with Type 2 diabetes. Diabet Med 2014;31:1121–1128
25. Yu MK, Katon W, Young BA. Associations between sex and incident chronic kidney disease in a prospective diabetic cohort. Nephrology (Carlton) 2015;20:451–458
26. Bjornstad P, Cherney DZ. Renal hyperfiltration in adolescents with type 2 diabetes: physiology, sex differences, and implications for diabetic kidney disease. Curr Diab Rep 2018;18:22
27. Shen Y, Cai R, Sun J, et al. Diabetes mellitus as a risk factor for incident chronic kidney disease and end-stage renal disease in women compared with men: a systematic review and meta-analysis. Endocrine 2017;55:66–76
28. Nelson RG, Morgenstern H, Bennett PH. Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. Am J Epidemiol 1998;148:650–656
29. Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC. Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. Diabetes Care 1999;22:944–950
30. Jenkins AJ, Lyons TJ, Zheng D, et al.; DCCT/EDIC Research Group. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int 2003;64:817–828
31. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
32. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357
33. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
34. Mann JFE, Ørsted DD, Brown-Frandsen K, et al.; LEADER Steering Committee and Investigators. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med 2017;377:839–848
35. Heerspink HJL, Parving HH, Andress DL, et al.; SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet 2019;393:1937–1947
36. Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al.; Ellipse Trial Investigators. Liraglutide in children and adolescents with type 2 diabetes. N Engl J Med 2019;381:637–646
37. Lytvyn Y, Bjornstad P, van Raalte DH, Heerspink HL, Cherney DZI. The new biology of diabetic kidney disease-mechanisms and therapeutic implications. Endocr Rev 2020;41:bnz010